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ORIGINAL ARTICLE

Symptomatic ventricular tachyarrhythmia is associated with delayed gadolinium enhancement in cardiac magnetic resonance imaging and with elevated plasma brain natriuretic peptide level in hypertrophic cardiomyopathy

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Summary
Background: Delayed gadolinium enhancement (DGE) in cardiac magnetic resonance (CMR) imaging indicates the areas with myocardial fibrosis, which are suggested to be arrhythmogenic substrate in hypertrophic cardiomyopathy (HCM). Elevated brain natriuretic peptide (BNP) is associated with cardiovascular events in HCM. We investigated the grade of DGE in CMR and plasma BNP levels in HCM patients with or without symptomatic ventricular tachycardia (VT) or ventricular fibrillation (VF).
Methods and results: We recruited 26 consecutive untreated HCM patients without any symptoms of heart failure. They were divided into 2 groups: (1) patients with symptomatic VT/VF [VT/VF(+) group, $n = 6$]; (2) patients without symptomatic VT/VF [VT/VF(−) group, $n = 20$]. CMR was performed to evaluate left ventricular geometry and the grade of DGE. Plasma BNP levels, left ventricular mass index, and the number of segments with positive DGE were greater in the VT/VF(+) group than in the VT/VF(−) group (698.1 ± 387.6 vs. 226.9 ± 256.8 pg/ml, $p = 0.006$; 152.3 ± 49.5 vs.

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89.5 ± 24.1 g/m^2, $p = 0.003$; 9.7 ± 5.7 vs. 3.5 ± 3.3, $p = 0.013$). On logistic regression, adjusted odds ratio for symptomatic VT/VF was 214 for log BNP (95% confidence interval [CI] 1.2—37,043, $p = 0.04$) and 1.54 for DGE score (95% CI 1.01—2.34, $p = 0.04$). *Conclusions:* High plasma BNP levels and the enlarged area of DGE in CMR were associated with symptomatic ventricular tachyarrhythmia. These factors may be useful markers for detecting high-risk patients of sudden cardiac death in HCM.

Introduction

The great threat from hypertrophic cardiomyopathy (HCM) is sudden cardiac death especially in children and young adults. The incidence is certainly low at 2—3% per year in adults and 4—6% in children, but risk stratification of sudden death is a major diagnostic challenge [1]. It is generally believed, although not established, that sudden cardiac death is due to ventricular arrhythmia [2]. The risk of sudden cardiac death increases with clinical risk factors such as non-sustained ventricular tachycardia (VT), syncope, exercise blood pressure response, family history of sudden death, extreme left ventricular hypertrophy (LVH), marked left ventricular (LV) outflow tract obstruction, and coronary microvascular dysfunction [1,3,4]. These markers have high negative predictive accuracy, but low positive predictive accuracy [1]. Thus, more sensitive markers of high-risk patients are needed.

Delayed gadolinium enhancement (DGE) in cardiac magnetic resonance (CMR) imaging is indicative of the areas with replacement scarring, which could be an arrhythmogenic substrate, in patients with HCM [5]. DGE in CMR has been reported to be associated with markers of sudden death [6] and VT detected by Holter monitoring [7,8] in HCM. However, there are no data that indicate the association of DGE in CMR and symptomatic sustained VT/ventricular fibrillation (VF).

Plasma brain natriuretic peptide (BNP) level is increased in patients with HCM [9]. Plasma BNP/N-terminal (NT) pro-BNP concentration has been shown to correlate with risk factors of sudden death such as LV wall thickness [10—14], LV outflow tract obstruction [13,15], or silent myocardial ischemia [16] in patients with HCM. Plasma NT pro-BNP levels were associated with clinical deterioration, defined as a composite of cardiovascular death and hospitalization for worsening heart failure symptoms in HCM patients with New York Heart Association (NYHA) functional class I—III [17]. However, it is unknown whether plasma BNP levels are useful in identifying high-risk patients in HCM without heart failure. Moreover, the relationship between plasma BNP levels and DGE in CMR has not been reported to date.

In this study, we analyzed HCM patients without symptoms of heart failure in order to define whether DGE in CMR or plasma BNP levels are associated with symptomatic ventricular tachyarrhythmia.

Methods

Patients characteristics

We studied 26 consecutive patients who were newly diagnosed as HCM. They were free from any symptom of heart failure (NYHA class I) (18 men, 8 women; mean age 67 ± 12 years) and took no medications. The diagnosis of HCM was based on the typical clinical, electrocardiographic, and hemodynamic features, with echocardiographic demonstration of nondilated, asymmetrically hypertrophied left ventricle in the absence of other cardiac or systemic disease that may produce LV hypertrophy [18,19]. Twenty patients were referred to the Hospital of Hyogo College of Medicine because of incidentally found ECG abnormality [VT/VF(−) group]. No patients had histories of syncope or cardiac arrest in this group. Six patients were referred to our hospital because of symptomatic sustained VT or VF [VT/VF(+) group]. Among these patients, three were survivors of VF. The other 3 patients had histories of syncope and were proven to have sustained VT by Holter monitoring or electrophysiological studies. Exclusion criteria were organic coronary stenosis, valvular heart disease, or systemic hypertension (≥140/90 mmHg). Plasma BNP concentration was measured using noncompetitive immunoradiometric assays for human BNP (Shionogi, Osaka, Japan).

Echocardiography

In all patients, conventional M-mode and 2-dimensional echocardiographic study with Doppler color flow imaging was performed by experienced

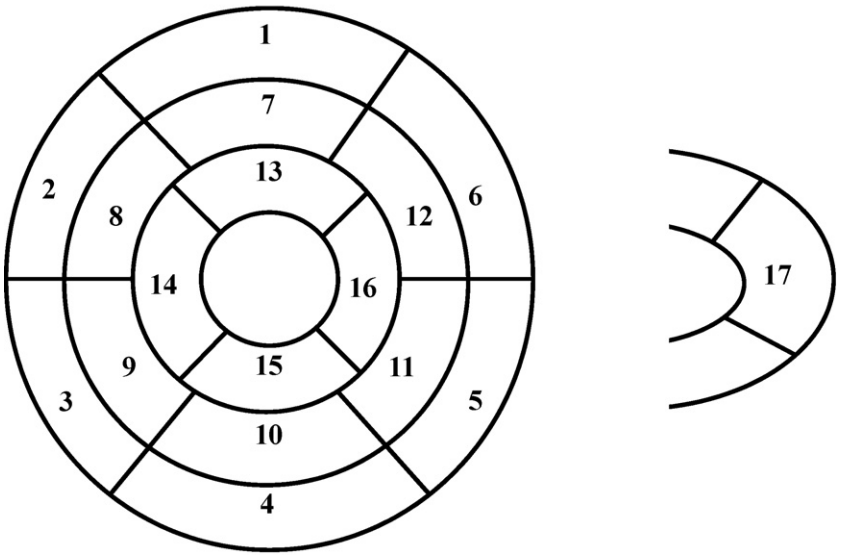

Figure 1 The schematic represents the segmentation as recommended by the American Heart Association and the American College of Cardiology [21]. Sixteen segments were evaluated in short-axis view (6-basal, 6-mid, 4-apical), and 1 segment was evaluated in long-axis view (1-apex).

sonographers. Asymmetric septal hypertrophy was defined as the thickness of septum/free wall $\geq$1.3. The presence of the intraventricular pressure gradient was evaluated with continuous-wave Doppler using a simplified Bernoulli equation ($\triangle P = 4v^2$, where P is pressure and v is flow velocity). Obstructive HCM (HOCM) was defined as a presence of an intraventricular pressure gradient of greater than 30 mmHg [20].

CMR technique and image analysis

CMR (Philips Intera 1.5T, Best, Netherlands) was performed using steady-state, free precession breath-hold cines in the long-axis planes and sequential 8-mm short-axis slices from the atrioventricular ring to the apex. The DGE images were acquired 15 min after intravenous diethylene triamine pentaacetic acid (DTPA, 0.1 mmol/kg) in the identical short-axis planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium.

LV mass and visual signal analysis was performed on an off-line work station (Virtual Place, Aze, Tokyo, Japan). LV function was analyzed from the serial short-axis cine loops using manual segmentation. End-systolic volume (ESV), end-diastolic volume (EDV), LV ejection fraction (LVEF), interventricular septal wall thickness (IVST), and LV mass index (LVMI) were calculated. For the DGE image, hyperenhancement was considered to be present only if it was also present in the same slice after swapping phase encoding; thus artifact was excluded. The grade of DGE was evaluated using the standard LV 17-segment model [21] (Fig. 1). Presence or absence of DGE was visually judged by the consensus of two observers, and the number of LV-segments with hyperenhancement was defined as DGE score.

Statistical analysis

Values are expressed as means $\pm$ S.D. All statistical analyses were performed using a commercially available statistical software (STATVIEW version 5.0, SAS Institute Inc., Cary, NC, USA). Comparison of variables between the 2 groups was performed by using Mann—Whitney U-test. Evaluation of differences between proportions was performed by Chi-square test. Linear regression analysis was performed to correlate DGE in CMR, LVMI, and plasma BNP levels. Non-adjusted and adjusted odds ratio that explains symptomatic sustained VT/VF was assessed with univariate and multivariate logistic analysis. Multivariate logistic regression model included DGE in CMR and plasma BNP levels. LVMI was not included because it was highly correlated with DGE in CMR. BNP data were subjected to logarithmic transformation (log) in these analyses because they were not normally distributed. We took p-value < 0.05 to be statistically significant.

Table 1 Patient characteristics

	VT/VF(+)	VT/VF(−)	*p*-Value
N	6	20	NS
Age (years)	55 ± 16	71 ± 8	$p = 0.023$
Male gender (*n*)	4	14	NS
HOCM (*n*)	1	5	NS
APH (*n*)	2	7	NS
ASH (*n*)	3	5	NS
BNP (pg/ml)	698.1 ± 387.6	226.9 ± 256.8	$p = 0.0062$
Echocardiographic data			
LAD (mm)	43 ± 8	41 ± 7	NS
LVDd (mm)	46 ± 3	46 ± 5	NS
LVDs (mm)	27 ± 5	28 ± 5	NS
IVST (mm)	18 ± 7	13 ± 4	NS
EF (%)	67 ± 6	68 ± 8	NS
E velocity (m/s)	54 ± 18	69 ± 21	NS
E/*A* ratio	0.97 ± 0.40	0.97 ± 0.46	NS
E′	4 ± 1	5 ± 2	NS
E/*E*′ ratio	16.1 ± 9.6	14.4 ± 5.4	NS
E deceleration time (ms)	293 ± 70	239 ± 82	NS

VT, ventricular tachycardia; VF, ventricular fibrillation; HOCM, hypertrophic obstructive cardiomyopathy; APH, apical hypertrophic cardiomyopathy; ASH, asymmetric septal hypertrophy; LAD, left atrial dimension; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end systolic diameter; IVST, interventricular septal thickness; EF, ejection fraction. Values are mean ± S.D.

Results

Patients were younger in the VT/VF(+) group than in the VT/VF(−) group (Table 1). There were no differences in gender and cardiac morphology assessed with conventional echocardiography between the 2 groups. Plasma BNP was higher in the VT/VF(+) group than in the VT/VF(−) group.

Fig. 2 shows a representative case in the VT/VF(−) group with low plasma BNP concentration and low DGE score. Fig. 3 shows a representative case in the VT/VF(+) group with high plasma BNP concentration and high DGE score.

There were no significant differences in CMR parameters of cardiac geometry such as EDV, ESV, LVEF, and IVST between the VT/VF(+) group and the VT/VF(−) group (Fig. 4A–D). However, LVMI and the number of segments with positive DGE were greater in the VT/VF(+) group than in the VT/VF(−) group (152.3 ± 49.5 vs. 89.5 ± 24.1 g/m^2, $p = 0.003$; 9.7 ± 5.7 vs. 3.5 ± 3.3, $p = 0.01$) (Fig. 4E and F). DGE score was correlated with LVMI ($r = 0.48$, $p = 0.01$). The correlation between plasma BNP level and LVMI or DGE score did not reach statistical significance($r = 0.363$, $p = 0.07$; $r = 0.37$, $p = 0.06$, respectively). In the study population, non-adjusted odds ratio for symptomatic VT/VF was 64.2 for log BNP (95% confidence interval [CI] 1.7–2419.6, $p = 0.02$), 1.42 for DGE score (95% CI 1.04–1.96, $p = 0.03$) and 1.07 for LVMI (95% CI 1.01–1.12, $p = 0.02$). Adjusted odds ratio for symptomatic VT/VF was 214 for log BNP (95% CI 1.2–37043, $p = 0.04$), 1.54 for DGE score (95% CI 1.01–2.34, $p = 0.04$).

Discussion

Enlarged area of DGE in CMR was associated with symptomatic VT/VF. This finding is compatible with the previous reports that showed the relationship between the size of DGE in CMR and non-sustained (NS)/sustained VT documented by Holter monitoring [7,8]. However, Dimitrow et al. have reported that the extent of DGE was not different between patients with NSVT and those without NSVT even though DGE in CMR was more frequently observed in patients with NSVT than those without NSVT [22]. However, 87% of their study population presented with dyspnea or exercise-induced angina pectoris, while our patients were free from chest symptoms. Usefulness of DGE in CMR for predicting life-threatening arrhythmia may be limited in HCM patients with symptoms of heart failure and angina. Further studies are necessary. Gadolinium-DTPA has been shown to distribute to extracellular space and cannot cross the intact sarcolemmal membrane [23]. Tissue volume is predominantly intracellular in the normal myocardium (75–80%) [24]; thus, the distribution volume of gadolinium is low in the normal heart. Extracellular space is expanded in the presence of collagenous scar

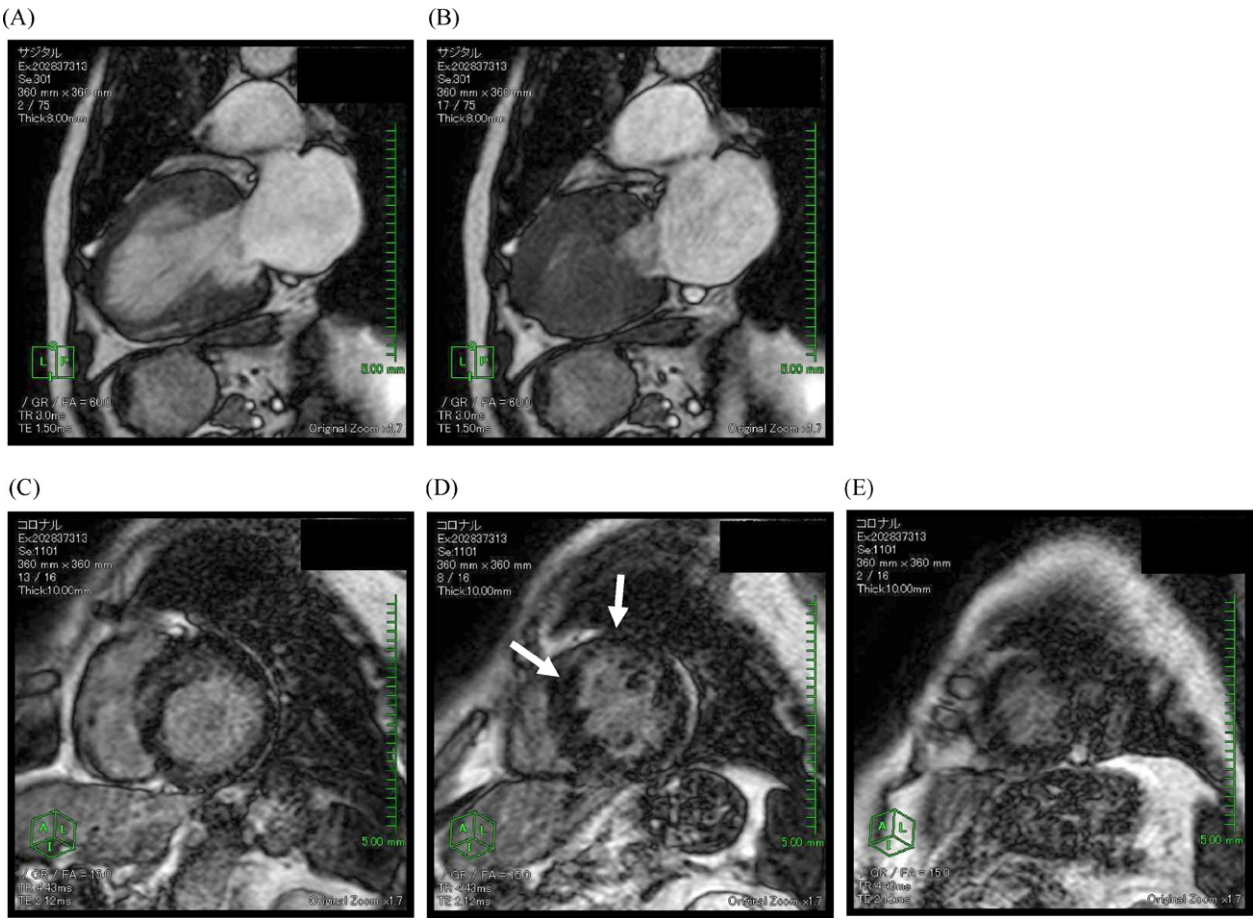

Figure 2 Representative findings of a patient with HCM without symptomatic VT/VF. A 70-year-old male patient was referred to our hospital because of cardiac murmur and ECG abnormality. He was diagnosed as hypertrophic obstructive cardiomyopathy with echocardiography. Plasma BNP concentration was 110 pg/ml and DGE score was 2. Long-axis view at (A) end-systolic period and (B) end-diastolic period in cine-mode. Obstruction of left ventricular outflow tract was observed in systolic phase. DGE images at (C) base, (D) mid, and (E) apical levels in the short-axis view are shown. Arrows indicate DGE positive segments that were found in the mid level of the short-axis view (segments 7 and 8).

to increase the gadolinium concentration in the tissue. Thus, it has been postulated that DGE in CMR analysis is predominantly located in the area where viable myocytes are absent and replaced by fibrosis in patients with HCM. Distribution of DGE corresponded well to that of myocardial scarring in necropsy in patients with HCM [5,6]. A case report has shown that the area of DGE in CMR represents regions of increased myocardial collagen but not disarray [25]. Myocardial scarring is thought to be caused by myocardial ischemia and used as a substrate of ventricular tachyarrhythmia [25]. Myocardial ischemia is common and multifactorial in HCM [1]. Major causes include impaired vasodilator reserve (perhaps related to the thickened and narrowed small intramural coronary arteries found in HCM) [4,26,27]; increased oxygen demand, especially in patients with severe myocardial hypertrophy and outflow gradients; and elevated filling pressures with resultant subendocardial ischemia [1,28—30]. Impaired coronary flow reserve can predict poor prognosis of HCM patients [4,28]. In our study population, both DGE and LVMI were increased in patients with symptomatic VT/VF, and DGE was highly correlated with LVMI. Myocardial ischemia induced by severe myocardial hypertrophy may cause VT/VF by forming myocardial scarring, an arrythmogenic subject. DGE in CMR should be a useful marker for predicting high-risk patients of sudden cardiac death in HCM.

We have also found, for the first time, that plasma BNP levels are higher in the VT/VF(+) group than in the VT/VF(−) group. Plasma BNP/NT pro-BNP concentration has been shown to correlate with magnitude of heart failure symptoms and exercise capacity [11—13], LV wall thickness [11—15], LV outflow tract obstruction [14,16], diastolic function [31,32], or silent myocardial ischemia [16] in

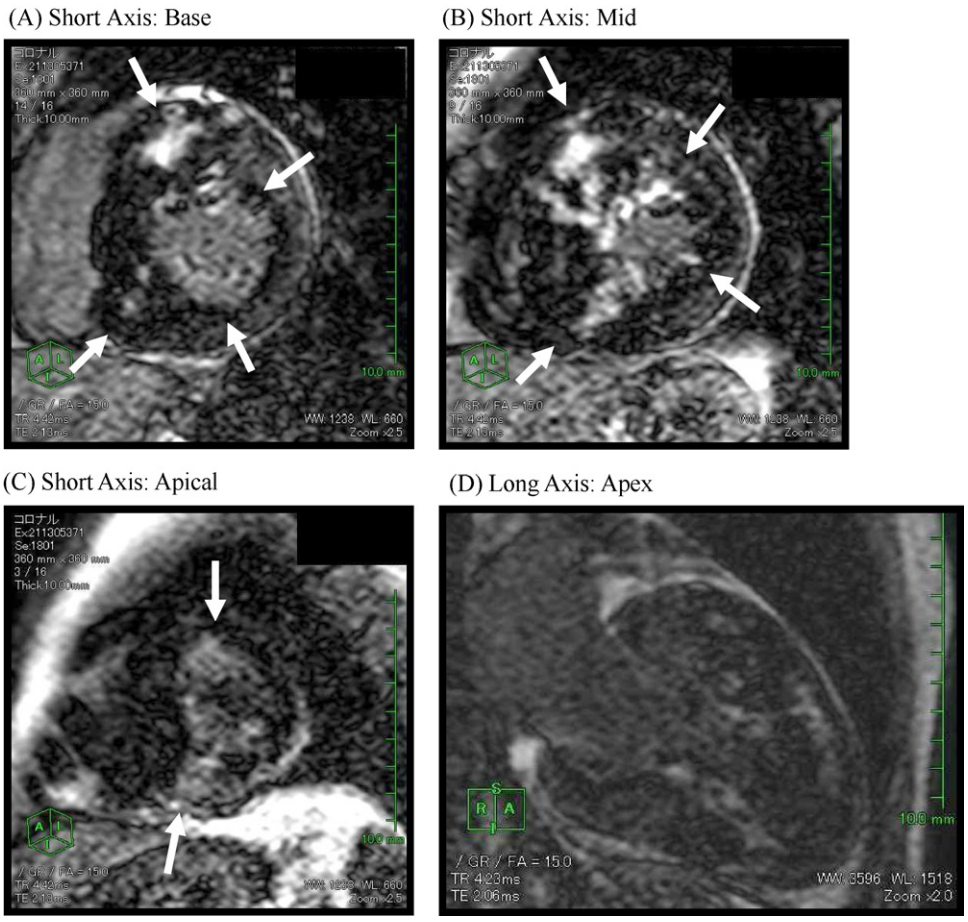

Figure 3 Representative findings of a patient with HCM with symptomatic VT/VF. A 35-year-old male patient was referred to our hospital because of sustained ventricular tachycardia. He was diagnosed with hypertrophic non-obstructive cardiomyopathy with echocardiography. Plasma BNP concentration was 711 pg/ml, and DGE score was 10. DGE images at (A) base, (B) mid, (C) apical levels in the short-axis view, and (D) apex in long-axis view are shown. Arrows indicate DGE positive segments that were found at base (segments 1, 3, 5, and 6), mid (segments 7, 9, 10 and 12), and apical levels (segments 13, and 15).

patients with HCM. There were no patients with symptoms of heart failure in our study population, and the incidence of LV outflow tract obstruction at rest was similar in the VT/VF(+) group and VT/VF(−) group. Thus, increased LVMI appears to be one of the causes of elevated plasma BNP concentration in our study population. However, the correlation between plasma BNP levels and LVMI was weak and did not reach statistical significance ($p = 0.07$). Thus, it remains unknown what is the major cause of different plasma BNP levels between VT/VF(+) group and VT/VF(−) group. So, what could be the cause of elevated plasma BNP levels in patients with VT/VF? We again speculate that myocardial ischemia could be the one. Hypoxia is a direct and sufficient stimulus for BNP induction in cardiomyocytes [33]. Plasma BNP levels are associated with silent myocardial ischemia detected by exercise scintigraphy [16]. Plasma BNP level may be increased by myocardial ischemia, which is exacerbated not only by LV hypertrophy but also by defective microcirculation in HCM patients. In our study population, the correlation between plasma BNP levels and DGE score was weak and did not reach statistical significance ($p = 0.06$). Plasma BNP level may be a marker of on-going ischemia, while DGE score may reflect both the intensity and duration of ischemia. Myocardial ischemia might cause VT/VF not only by scar formation in myocardium, but also by direct effect on cardiomyocytes in HCM.

Limitations of the study

Three limitations of the study are noted. First, the present study consisted of a small number of patients because we focused on symptomatic VT/VF, but not on NSVT detected by Holter monitoring. We did not perform receiver operating curve

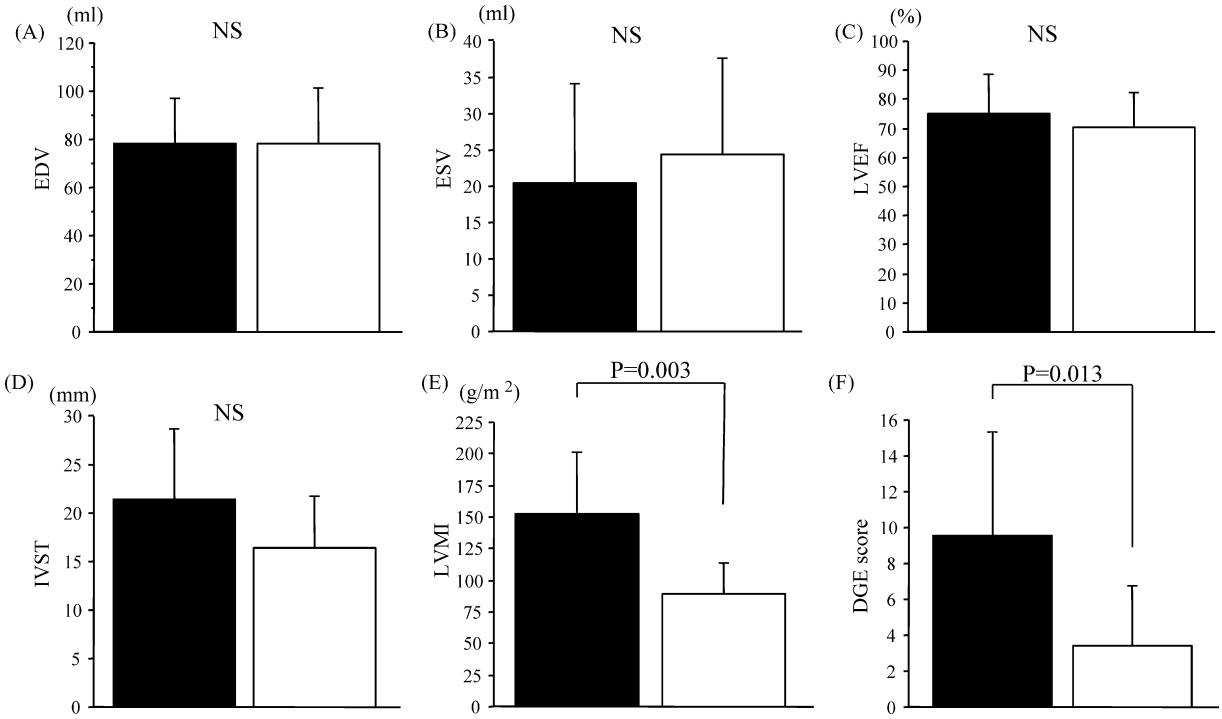

Figure 4 Parameters in cardiac magnetic resonance imaging of the VT/VF(+) group (black bars) and the VT/VF(−) group (white bars). (A) End-diastolic volume (EDV), (B) end-systolic volume (ESV), (C) left ventricular ejection fraction (LVEF), (D) interventricular septal wall thickness (IVST), (E) left ventricular mass index (LVMI), and (F) delayed gadolinium enhancement (DGE) score. Values are mean ± S.D.

analysis and multivariate logistic regression analysis with other known risk factors of sudden death such as age and LV outflow obstruction because of a small number of patients. Second, Holter monitoring was not performed in many patients without symptomatic VT/VF. However, NSVT in Holter monitoring has high negative predictive accuracy (approx. 90%), but low positive predictive accuracy (22% or lower) [1]. There may be some high-risk patients for sudden cardiac death in the VT/VF(−) group, but the number of high-risk patients may not be large. Finally, we did not evaluate myocardial ischemia in our study population. We speculated that myocardial ischemia may link the enlarged area of DGE in CMR, elevated plasma BNP levels, and symptomatic VT/VF. Further studies are necessary.

Conclusions

High plasma BNP levels and the enlarged area of DGE were associated with symptomatic ventricular tachyarrhythmia. These factors may be useful markers for detecting high-risk patients of sudden cardiac death in HCM.

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